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Clinical Trial Results

A Phase II Multi-Center Study of Bevacizumab in Combination with Ixabepilone in Subjects with Advanced Renal Cell Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Trial Information

- **ClinicalTrials.gov Identifier**: NCT00923130
- **Sponsor(s)**: National Cancer Institute (NCI)
- **Principal Investigator**: Tito Fojo
- **IRB Approved**: Yes

Lessons Learned

- Accrual to renal cell carcinoma trials remains a challenge despite the lack of prolonged response to the available treatments.
- The observation of three responses among the 30 patients with median progression-free survival and overall survival of 8.3 and 15 months, respectively, indicates the combination has some activity, but it is not sufficient for further development.

Abstract

Background. Treatment of metastatic renal cell carcinoma (mRCC) remains suboptimal. Preclinical data have previously shown that ixabepilone, a microtubule-stabilizing agent approved for the treatment of breast cancer, is active in taxane-sensitive and -resistant cells. In this single-arm phase II trial, we investigated a combination of ixabepilone plus bevacizumab in patients with refractory mRCC.

Methods. We enrolled 30 patients with histologically confirmed mRCC, clear cell subtype, who had not been previously treated with ixabepilone or bevacizumab but had received at least one prior U.S. Food and Drug Administration (FDA)-approved treatment for renal cell carcinoma (RCC). The treatment regimen consisted of 6 mg/m^2 ixabepilone per day for 5 days and 15 mg/kg bevacizumab every 21 days. After 6 cycles, the treatment interval could be extended to every 28 days. The primary endpoint was the objective response rate according to the Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and the toxicity of the combination.

Results. The median number of prior therapies was two (range per patient one to five). Patients received a median of 8 cycles of ixabepilone plus bevacizumab (range 2–54). The median follow-up was 36.4 months (range 23.5–96.5). Nineteen patients (63.3%) had stable disease as a best response. Three patients (10%) had a partial response. The median PFS was 8.3 months (95% confidence interval [CI], 4.9–10.6) and the median OS was 15.0 months (95% CI, 11.3–28.8). The total number of cycle for safety evaluation was 289. Grade 3/4 adverse events (>5% incidence) included lymphopenia (16.7%), hypertension (6.7%), and leukopenia (6.7%).

Conclusion. The combination of ixabepilone and bevacizumab was well tolerated, with modest activity in second - or later-line mRCC, but it is not recommended as a therapy without further clinical development. Alternative combinations with these agents could be explored in future studies. ***The Oncologist*** 2017;22:888–e84

Discussion

The unproven hypothesis that angiogenesis is a key step in the development and metastasis of solid tumors [1], especially mRCC [2], led to the development of a large number of agents whose putative target was the vascular endothelial growth factor (VEGF) pathway. Several of these agent were shown to have modest activity in the therapy of mRCC and this led to their approval by regulatory agencies. However, given their limited activity, their use in combinations has been extensively explored. We studied the combination of ixabepilone, a microtubule-targeting epothilone [3, 4], with bevacizumab, a monoclonal antibody that binds VEGF.

Preclinical data from several in vivo models including breast, kidney, lung, and colon cancers demonstrated increased

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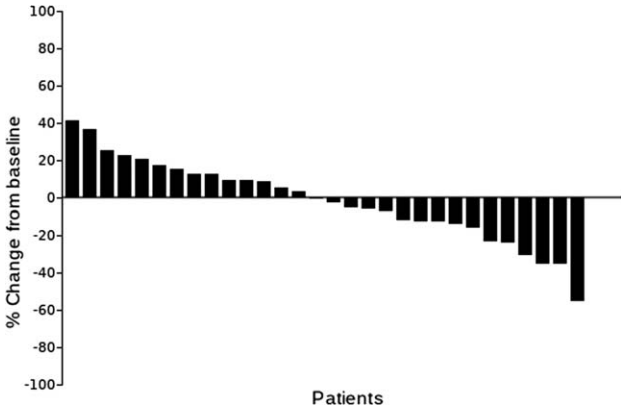
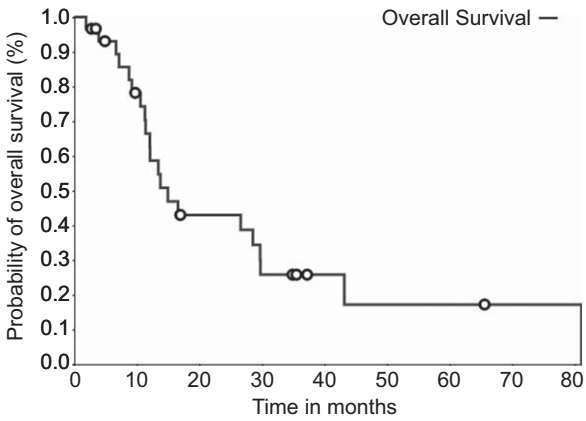


Best percentage change from baseline for target lesions per patient.



Months	0	10	20	30	40	50	60	70	80
No. at risk	30	19	10	6	3	2	2	1	1
No. censored	0	4	1	0	3	0	0	1	0

Overall survival measured in months. Patients were censored at the date last known alive, or if unknown, at the off-study date.

activity of ixabepilone in combination with bevacizumab, suggesting a synergistic effect in both antitumor and antiangiogenic activities and the absence of overlapping toxicities [5]. More recently, randomized trials reported acceptable activities and toxicities of combined therapy in platinum/taxane-resistant cervical-uterine [6] and locally recurrent or metastatic breast cancer [7].

This investigation was designed as a single-arm phase II multi-center trial with a primary aim of determining the objective response rate of ixabepilone plus bevacizumab using RECIST criteria in patients with relapsed or refractory mRCC. We also evaluated PFS, OS, and toxicities of the combined therapy. The observed activity of the combined therapy was less than originally expected, considering results in an earlier phase II study of ixabepilone in renal cancer that demonstrated an objective response rate of 13% [8]. Regarding side effects, the tested combination was well tolerated without major side effects or deaths related to treatment.

Despite the low response rate of 11.3%, the median PFS of 8.3 month and OS of 15 months compare favorably with putative antiangiogenic agents approved for mRCC in second-line treatment before 2015 [9–11]. Furthermore, with a median number of two previous lines of treatment, a majority of patients were receiving this treatment in third line, making this combination potentially active in the third-line setting. However, recent advances in immunotherapy for RCC restrict the potential scope of this combination.

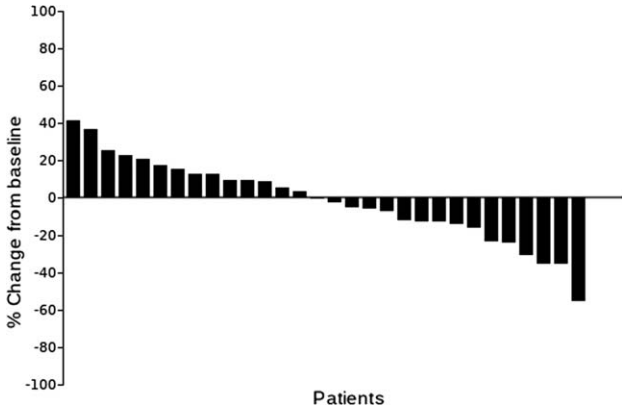
Trial Information	
Disease	Renal cell carcinoma – clear cell
Stage of Disease/Treatment	Metastatic/Advanced
Prior Therapy	1 prior regimen
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Overall survival
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Toxicity
Investigator's Analysis	Active but results overtaken by other developments

Drug Information for Phase II Ixabepilone + Bevacizumab	
Drug 1	
Generic/Working name	Ixabepilone
Trade name	Ixempra
Company name	Bristol-Myers Squibb

Drug type	Microtubule inhibitor
Drug class	Microtubule-targeting agent
Dose	6 milligrams (mg) per squared meter (m^2)
Route	IV
Drug 2	
Generic/Working name	Bevacizumab
Trade name	Avastin
Company name	Genentech/Roche
Drug type	Antibody
Drug class	Angiogenesis - VEGF
Dose	15 milligrams (mg) per kilogram (kg)
Route	IV

Patient Characteristics for Phase II Ixabepilone + Bevacizumab	
Number of patients, male	23
Number of patients, female	7
Stage	Metastatic or recurrent
Age	Median (range): 62.3 (44.3–78.8)
Number of prior systemic therapies	Median (range): 2 (1–5)
Performance Status: ECOG	0 — 2 1 — 24 2 — 4 3 — unknown —
Cancer Types or Histologic Subtypes	Clear cell, 30

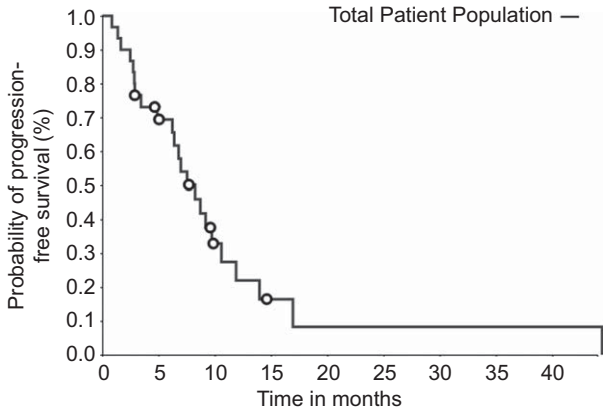
Primary Assessment Method for Phase II Ixabepilone + Bevacizumab	
Assessment	
Number of patients screened	40
Number of patients enrolled	30
Number of patients evaluable for toxicity	30
Number of patients evaluated for efficacy	30
Evaluation method	RECIST 1.1
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 3$ (10%)
Response assessment SD	$n = 19$ (63.3%)
Response assessment PD	$n = 8$ (26.7%)
Response assessment OTHER	$n = 0$ (0%)
(Median) duration assessments PFS	8.3 months, CI: 4.9–10.6
(Median) duration assessments OS	15.0 months, CI: 11.3–29.8
Kaplan-Meier Time units	Months



Best percentage change from baseline for target lesions per patient.

Secondary Assessment Method for Phase II Ixabepilone + Bevacizumab (PFS)	
Assessment	
Number of patients evaluated for efficacy	30
Kaplan-Meier Time units	months

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percentage at start of evaluation period	Kaplan-Meier %	No. at next evaluation/ No. at risk
0	0	0	100.00	100.00	30
0.85	1	0	100.00	96.67	29
1.38	1	0	96.67	93.33	28
1.64	1	0	93.33	90.00	27
2.49	1	0	90.00	86.67	26
2.85	1	0	86.67	83.33	25
2.89	1	1	83.33	79.86	23
3.44	1	0	79.86	76.39	22
4.66	0	1	76.39	76.39	21
4.89	1	0	76.39	72.75	20
5.05	0	1	72.75	72.75	19
6.23	1	0	72.75	68.92	18
6.39	1	0	68.92	65.09	17
6.79	1	0	65.09	61.26	16
6.98	1	0	61.26	57.44	15
7.54	1	0	57.44	53.61	14
7.70	0	1	53.61	53.61	13
8.26	1	0	53.61	49.48	12
8.72	1	0	49.48	45.36	11
9.18	1	0	45.36	41.24	10
9.61	0	1	41.24	41.24	9
9.74	1	0	41.24	36.65	8
9.87	0	1	36.65	36.65	7
10.59	1	0	36.65	31.42	6
11.90	1	0	31.42	26.18	5
13.97	1	0	26.18	20.95	4
14.62	0	1	20.95	20.95	3
16.95	1	0	20.95	13.96	2
44.43	1	0	13.96	6.98	1



Months	0	5	10	15	20	25	30	35	40
No. at risk	30	18	5	2	1	1	1	1	1
No. censored	0	3	3	1	0	0	0	0	0

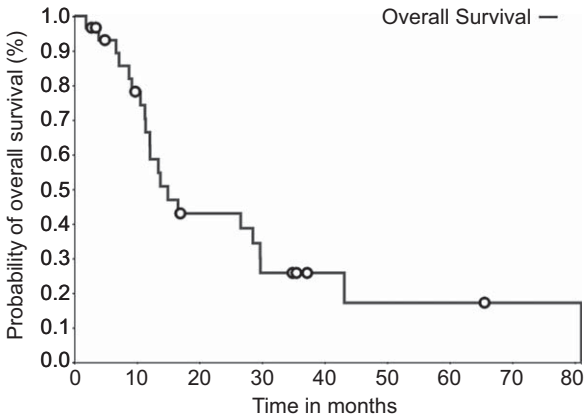
Based on Kaplan-Meier analysis, median progression-free survival was 8.3 months (95% CI: 4.9–10.6 months); median overall survival was 15.0 months (95% CI: 11.3–29.8 months); and median potential follow-up was 36.4 months (range 23.5–96.5 months). Patients were censored at the off-study date if they did not have documented disease progression.

Secondary Assessment Method for Phase II Ixabepilone + Bevacizumab (OS)

Assessment	
Number of patients evaluated for efficacy	30
Kaplan-Meier Time units	months

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/ No. at risk
0	0	0	100.00	100.00	30
1.87	1	0	100.00	96.67	29
2.75	0	1	96.67	96.67	28
3.44	0	1	96.67	96.67	27
3.90	1	0	96.67	93.09	26
4.89	0	1	93.09	93.09	25
6.69	1	0	93.09	89.36	24
7.18	1	0	89.36	85.64	23
8.72	1	0	85.64	81.92	22
9.18	1	0	81.92	78.19	21
9.74	0	1	78.19	78.19	20
10.59	1	0	78.19	74.28	19
11.28	1	0	74.28	70.37	18
11.41	1	0	70.37	66.46	17
12.07	1	0	66.46	62.55	16
12.10	1	0	62.55	58.64	15
13.44	1	0	58.64	54.73	14
13.77	1	0	54.73	50.83	13
14.98	1	0	50.83	46.92	12
16.56	1	0	46.92	43.01	11
16.95	0	1	43.01	43.01	10
26.59	1	0	43.01	38.71	9
28.52	1	0	38.71	34.40	8
29.70	1	0	34.40	30.10	7

29.74	1	0	30.10	25.80	6
34.89	0	1	25.80	25.80	5
35.51	0	1	25.80	25.80	4
37.21	0	1	25.80	25.80	3
43.15	1	0	25.80	17.20	2
65.57	0	1	17.20	17.20	1
81.02	1	0	17.20	0.00	0



Months	0	10	20	30	40	50	60	70	80
No. at risk	30	19	10	6	3	2	2	1	1
No. censored	0	4	1	0	3	0	0	1	0

Overall survival measured in months. Patients were censored at the date last known alive, or if unknown, at the off-study date.

Adverse Events: Phase II Ixabepilone + Bevacizumab

All Dose Levels, Cycle 1

Name	NC/NA	1	2	3	4	5	All Grades
Alopecia	90%	3%	7%	0%	0%	0%	10%
Anorexia	90%	7%	3%	0%	0%	0%	10%
Diarrhea	81%	13%	3%	3%	0%	0%	19%
Epistaxis	90%	10%	0%	0%	0%	0%	10%
Fatigue	74%	23%	3%	0%	0%	0%	26%
Hypertension	57%	20%	20%	3%	0%	0%	43%
Nausea	73%	17%	7%	3%	0%	0%	27%
Vomiting	87%	10%	3%	0%	0%	0%	13%
Alanine aminotransferase increased	90%	10%	0%	0%	0%	0%	10%
Aspartate aminotransferase increased	87%	13%	0%	0%	0%	0%	13%
Activated partial thromboplastin time prolonged	90%	3%	7%	0%	0%	0%	10%
Anemia	64%	23%	10%	3%	0%	0%	36%
Creatinine increased	83%	17%	0%	0%	0%	0%	17%
Hyperkalemia	87%	10%	3%	0%	0%	0%	13%
Hypoalbuminemia	60%	33%	7%	0%	0%	0%	40%
Hyponatremia	90%	10%	0%	0%	0%	0%	10%
Lymphocyte count decreased	53%	17%	13%	17%	0%	0%	47%
Neutrophil count decreased	90%	0%	7%	0%	3%	0%	10%
Platelet count decreased	90%	0%	0%	10%	0%	0%	10%
White blood cell decreased	77%	13%	3%	7%	0%	0%	23%
Hypophosphatemia	87%	0%	10%	3%	0%	0%	13%

Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion Study completed

Investigator's Assessment Active but results overtaken by other developments

Renal cell carcinoma is among the ten most frequently diagnosed cancers in the general population in the U.S. [2], with approximately 63,000 new cases and almost 14,000 deaths from RCC each year [12]. Given its refractory nature, mRCC remains a difficult problem with 5-year survival rates of 8% [2].

Interest in the angiogenesis hypothesis, especially its putative role in RCC led to the development of innumerable "antiangiogenic agents" that sought to interdict signaling through the VEGF pathway. Despite the approval of several similar agents for the treatment of mRCC by regulatory agencies, efficacy was modest and short-lived, in part due to the emergence of resistance [13]. This has provided the impetus to develop combination regimens using antiangiogenic agents in the hopes of improving therapeutic efficacy. For example, although initial studies with single-agent bevacizumab in patients with mRCC demonstrated a significant increase in time to progression [14], its efficacy was not consider sufficient for use as a single agent. It was then explored and subsequently approved by regulatory agencies for the treatment of mRCC in combination with interferon alfa, based on the results of a phase III trial [15]. With this background, we embarked on a clinical trial exploring the activity of the combination of bevacizumab with ixabepilone. In preclinical studies, ixabepilone, a non-taxane microtubule-stabilizing agent, had been shown to be active against cancer cell lines intrinsically insensitive to taxanes as well as cell lines that had developed resistance. To date, the only regulatory approval for ixabepilone is in metastatic breast cancer as a monotherapy or in combination with capecitabine based on an open-label phase III trial that enrolled 752 patients [16].

In mRCC, we initially explored the activity of ixabepilone monotherapy in previously untreated patients [8] using the same schedule of administration—6 mg/m^2/day, for 5 consecutive days every 3 weeks—used in combination with bevacizumab in this trial. In the previous trial, the overall response rate was 13% with a median duration of response of 5.5 months and an OS of 19.25 months [8]. This regimen is different from that approved in breast cancer (40 mg/m^2 every 3 weeks) and was chosen because of the lower rate of neurotoxicity. Another phase II trial with the 40 mg/m^2 every 3 weeks was published with 12 patients and no objective responses [17]. Given that both ixabepilone and bevacizumab had demonstrated modest activity in mRCC, appeared not to have overlapping toxicities, and had shown encouraging activity in preclinical models, we chose to explore the combination of ixabepilone plus bevacizumab in mRCC. The results demonstrated the combination was well tolerated with modest activity.

In our view, the recent approval of cabozantinib [18] and especially nivolumab [19] for the therapy of mRCC in second line [2] make the further development of the tested combination very difficult. Accrual for this trial that began in 2009 was challenging and would be even more challenging in 2017.

Disclosures

The authors indicated no financial relationships.

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